PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	
SATO ET AL.	Group Art Unit: 1642
Serial No. 09/720,326	Examiner: Karen A. Canella
Filed: December 22, 2000	**Mail Stop AF**
For: THERAPEUTIC AGENT FOR HYPERCALCEMIC CRISIS	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION UNDER 37 C.F.R. § 1.132

We, Toshiaki Tsunenari, Hidemi Saito, and Etsuro Onuma, declare and state as follows:

1. I, Toshiaki Tsunenari, am a co-inventor of the above-identified application. We are colleagues at Pharmaceutical Research Dept. 4, Kamakura Research Labs., Chugai Pharmaceutical Co., Ltd.

2. I have read and understood application Serial No. 09/720,326, including pending claims 1, 4, 6, 9-16, 19-21, and 33, and new claims 34-42. The present invention is directed to methods for treating hypercalcemic crisis using a humanized anti-PTHrP antibody capable of inhibiting the binding between PTHrP and a receptor thereof.

3. I understand that the Examiner has rejected the claims as obvious over various combinations of the *Seger*, *Sato*, *Potts*, *Scholm*, and *Gristina* references. However, none of those references teaches or suggests the use of any agents to treat hypercalcemic crisis. In fact, one of the cited references, *Potts* acknowledges the shortcomings of hypercalcemia agents for the treatment of hypercalcemic crisis. As discussed in the specification, it was well recognized that traditional treatments for hypercalcemia did not effectively treat hypercalcemic crisis. *See* specification page 3, lines 13-23.

4. The present invention was developed to treat hypercalcemic crisis. Prior art treatments for hypercalcemia were generally viewed as ineffective treatments for hypercalcemic crisis. Thus, nothing in the prior art would have predicted the ability of humanized PTHrP antibodies to effectively treat hypercalcemic crisis.

5. The attached experimental protocol and data show that a humanized anti-PTHrP antibody effectively treats hypercalcemic crisis, whereas other treatments for simple hypercalcemia do not. The experiment used a rat that showed the marginal calcium concentration and was in condition of hypercalcemic crisis. Rats were treated with humanized anti-PTHrP antibody (CAL), calcitonin (eCT), or bisphosphonate (ALN), and blood calcium levels were measured at different time intervals for 7 days after administration. Treatment of hypercalcemic crisis in this model requires a rapid and persistent lowering of blood calcium levels.

6. The results of this experiment show that only the anti-PHTrP antibody was effective at quickly and persistently lowering calcium levels in the rat model. The

bisphosphonate did not act quickly enough, and provided an effect too slow to treat hypercalcemic crisis. The calcitonin, on the other hand, acted quickly, but produced only a transient effect. Thus, unlike other hypercalcemic agents, the PTHrP antibody is unexpectedly effective at treating hypercalcemic crisis.

7. Accordingly, I conclude that before the filing date of the present invention, a person skilled in the art would not have expected the hypercalcemic agents, including the PTHrP antibody, to be an effective treatment for hypercalcemic crisis. Applicants finding that the humanized PTHrP antibody can effectively treat hypercalcemic crisis is surprising and is neither taught nor suggested by any of the *Seger*, *Sato*, *Rotts*, *Scholm*, or *Gristia* references.

8. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: Dec. 21, 2004

By: Toshiaki Tsunenari
Toshiaki Tsunenari

Hidemi Saito
Hidemi Saito

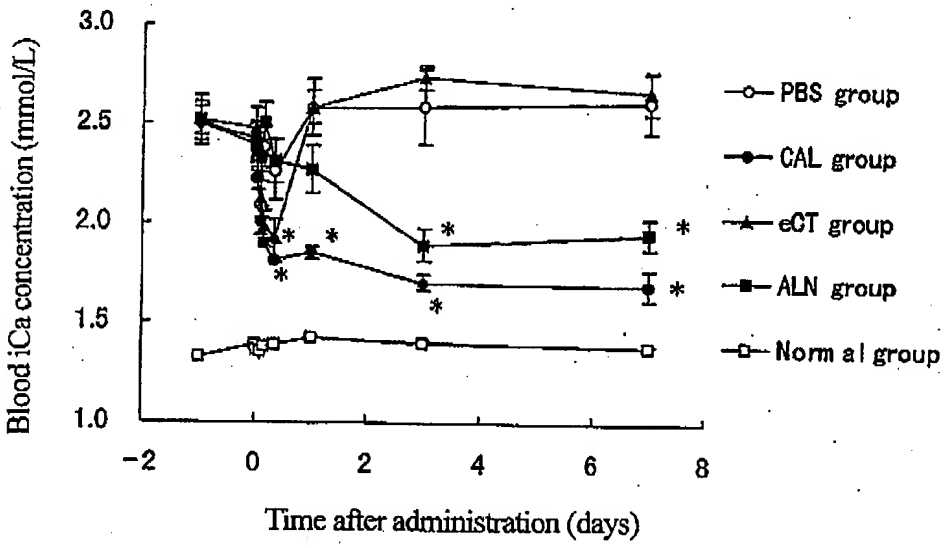
Etsuro Onuma

Etsuro Onuma

Comparison of Humanized anti-PTHrP Antibody (CAL) and Other Hypocalcemic Agents, Calcitonin (eCT) and Bisphosphonate (alendronate, ALN)

The amelioration effect of humanized anti-PTHrP antibody (CAL) and other hypocalcemic agents, calcitonin (eCT) and bisphosphonate (alendronate, ALN) on blood iCa concentration were determined using rat models suffered from humoral hypercalcemia with malignancy (HHM). The HHM rat model had about 2.5 to 2.6 mmol/L of blood iCa concentration (21 to 22 mg/dl blood Ca concentration). The rat will die at about 3.0 mmol/L of blood iCa concentration, so we considered this model rat showed the marginal calcium concentration and was clearly in condition of hypercalcemic crisis.
To this model rat, 3.0 mg/kg of CAL, 10 U/kg of eCT, or 5.0 mg/kg of ALN were administered intravenously as single dose. The blood calcium concentration after administration was determined at specified time intervals.
The results were shown below:

Figure: Blood iCa concentration after single administration over time



There were 5 animals for each group. Each value represents ± SE.
mmol/l iCa × 4.008 = mg/dl Ca (2.5 to 2.7mmol/L iCa corresponds 21 to 22 mg/dl blood calcium)

The above figure demonstrated that CAL and calcitonin (cCT) had similar, rapid onset of hypocalcemic effects, but the effect of CAL persisted for far longer (about 1 week). As for eCT, the calcium concentration was raised after 24 hours of the administration of eCT, which shows immediate but transient effect. In contrast, the maximum effect of alendronate (ALN) was not seen for 72 hours. ALN is known that it is required 2 or 3 days for the expression of its effect. Accordingly, it is revealed that the CAL can act immediately and continuously on decreasing the blood iCa concentration and may be a potent drug for hypercalcemic crisis. On the other hand, the known hypercalcemic agents calcitonin and alendronate (bisphosphonate) may be not so potent for treating hypercalcemic crisis.